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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 02/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/463,320	PELED ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cov r sh t with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7-13,15,37,39,42-45 and 47-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7-13,15,37,39,42-45 and 47-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/09/03 has been entered.

Claims 1-2, 4-5, 7-13,15, 37, 39, 42-45 and 47-57 are pending and under consideration in the instant application.

In view of the amendment, filed 12/09/03 and declaration of Dr. Eitan Fibach under 37 CFR 1.132 the following rejection remains

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-2, 4-5, 7-13,15, 37, 39, 42-45 and 47-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore et al(Blood Cells, 1994, v.20, pages 468-481) or C.De Bruyn et al., (Stem Cells 1995, v.13, pages 281-288) each in view of Cicuttine et al (Blood, 1992, v 80, pp 102-112) and of Percival et al (J Nutrition, 1992, v122 pages 2424-2429) for the same reasons set forth in the previous Office Action, mailed 08/11/03.

Applicant's arguments, filed 12/09/03 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) neither Moore nor De Bruyn teach or suggest reducing the capacity of the hematopoietic cells in utilizing copper to inhibit differentiation during ex-vivo expantion using a transition metal chelator such as TEPA; (ii). Percival et al does not cure the fatal deficiencies of Moore and De Bruyan since Percival et al does not say that TEPA inhibits differentiation. The effects of adding TEPA to the HL-60 cells were assessed by measuring the activity of the copper-containing enzymes CU/An superoxide. The decrease in CuZn SOD activity was attributed to chelation of the copper required for the enzyme to function that is not an indicator of differentiation.

Contrary to Applicant's assertion it appears that applicant and the examiner differ on interpretation of both the claimed methods and the prior art. Also, applicant relies upon an asserted and claimed mechanism of action but does not provide objective evidence how the prior art teaching of the same culturing condition using the same step and the same reagent differs from the claimed methods. It is unclear how the method taught by Percival et al. using a step of providing hematopoietic cells with TEPA differ from the claimed method. Therefore, it is clear that both Percival et al. and applicant administer the same reagent, that is TEPA to hematopoietic cells to achieve the same results. It is acknowledged that applicant now recites and believes in a different mechanism of action than the prior art. However, the instant methods do not negate or preclude the mechanism of action indicated by the prior art nor does applicant provide objective evidence to distinguish the prior art from the claimed invention. Moreover, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Even though applicant has proposed or claimed the mechanism by which TEPA acted on hematopoietic cells, it does not appear to distinguish the prior art teaching the same or nearly the same methods to achieve the same end result. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. However, Applicant cited the second publication of Percival et al , wherein it is clearly stated that " if copper is essential for differentiation then chelation of copper with TEPA should prevent the cell from differentiation" (see Applicant argument filed 12/09/03 page 12 in particular). Clearly one skill in the art would be aware of the fact that a transition metal chelator TEPA might be used to inhibit differentiation.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Moore et al. teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient (see, entire document, abstract in particular). Moore et al. teach that the hematopoietic stem cells can be derived from umbilical cord blood (see page 469 in particular). Moore et al. teach a growth medium with nutrients and early and late acting cytokines (See Material and Methods in particular). Moore et al. teach that ex vivo expansion of cord blood CD34+/CD38- cells will permit improved engraftment of adults (see abstract in particular).

Similarly, C.De Bruyn et al. teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining $CD34^{+}$ hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient (see, entire document, abstract in particular) C.De Bruyn et al. teach that the hematopoietic stem cells can be derived from umbilical cord blood or from bone marrow (see Page 282, in particular). Moore et al. teach a growth medium with nutrients and early and late acting cytokines (See Material and Methods in particular).

Moore et al. or C.De Bruyn et al. does not explicitly teach a method of hematopoietic cell transplantation and method of adoptive immunotherapy, under define growth conditions for cell proliferation and with a transition metal chelator , such as TEPA having an affinity for copper wherein said chelator inhibits differentiation of said cells.

Cicuttine et al. teach a method of coculturing hematopietic progenitor cells using define growth condition that will stimulate growth while inhibit differentiation (see entire document, page 104, column 2 in particular). The growth media containing nutrients, early and late acting cytokines and zinc. As taught by Cicuttine et al. (see Discussion in particular) zinc has an affinity to copper and thus would reduce copper utilization of culturing hematopoietic cells. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made that culturing the cell in the medium containing zinc would reduce a capacity of hematopoietic cells in utilizing cooper, absent a showing of unobvious property.

Percival et al. teach culturing condition using define growth medium condition that will stimulate growth while inhibit differentiation. (see entire document, Abstract in particular). Percival et al. teach that cells can be made copper deficient by incubating them in the media containing 50 μM TEPA (see Material and Methods in particular). Percival et al. teach that copper is essential for the process of differentiation and chelating cooper with tetraethylenepentamine will inhibit differentiation (see page 2428 in particular).

Moreover, Applicant acknowledge that Percival et al. teach that cells can be made copper deficient by incubating them in the media containing tetraethylenepentamine without loss of viability or alteration in the stage of differentiation (see page 13 of Applicant's arguments, filed 06/11/03 , Paper No. 25 in particular). This supports the examiner position that TEPA support proliferation while inhibiting differentiation.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Cicuttine et al. and Percival et al. and to those of Moore et al. or C.De Bruyn et al. to obtain a claimed method of hematopoietic cell transplantation and method of adoptive immunotherapy, under define growth conditions for cell proliferation and with a transition metal chelator , such as TEPA having an affinity for copper wherein said chelator inhibits differentiation of said cells.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because cultivating cells under growth conditions for reducing a capacity in utilizing copper using zinc containing medium or using a TEPA as a transition metal chelator having an affinity for copper will support only growth, proliferation and expansion without inducing differentiation of said cells will support only growth, proliferation and expansion without inducing differentiation of said cells as taught by as taught by Cicuttine et al. and Percival et al. that can be further used a method of hematopoietic cell transplantation and method of adoptive immunotherapy, comprising obtaining hematopoietic cells from a donor, ex-vivo expansion of said cells and transplanting said cells to a patient as taught by Moore et al. or C.De Bruyn et al.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claim 52 - 57 are included because the claimed dosage of transition metal chelator from about 0.1 μM to about 100mM, or from about 4 μM to about 50 mM, from about 5 μM to about 40 mM overlaps the referenced 50 μM of TEPA and is therefore an obvious variation of the reference teaching absent a showing of unobvious property. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

4. No claim allowed

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

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January 26, 2004

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